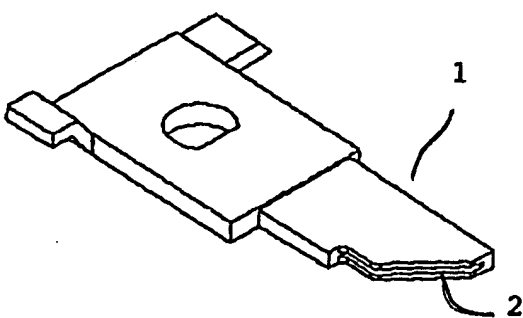




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>G01N 21/03, B01L 3/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/36765</b> <b>(43) International Publication Date:</b> 22 July 1999 (22.07.99)
<b>(21) International Application Number:</b> PCT/SE99/00046 <b>(22) International Filing Date:</b> 14 January 1999 (14.01.99) <b>(30) Priority Data:</b> 9800070-6      14 January 1998 (14.01.98)      SE <b>(71) Applicant (for all designated States except US):</b> HEMOCUE AB [SE/SE]; P.O. Box 1204, S-262 23 Ängelholm (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SVENSSON, Johnny [SE/SE]; Nordala 3031, S-262 73 Ängelholm (SE). NILSSON, Bertil [SE/SE]; Storkvägen 10, S-237 37 Bjärred (SE). OLSSON, Per [SE/SE]; Svedjegatan 11, S-260 80 Munka Ljungby (SE). JANSSON, Lars [SE/SE]; Råggatan 2, S-262 53 Ängelholm (SE). <b>(74) Agent:</b> AWAPATENT AB; P.O. Box 5117, S-200 71 Malmö (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>In English translation (filed in Swedish).</i>
<b>(54) Title:</b> MIXING METHOD  <b>(57) Abstract</b> <p>The invention relates to a method for carrying out mixing in a thin liquid layer, which is arranged between essentially parallel walls at a capillary distance from each other. The mixing is carried out by subjecting the walls to a motion essentially in the plane of the liquid layer, balancing the motion against the capillary force exerted by the walls on the liquid, and selecting the interface between the liquid layer and the surrounding medium so that it functions as an elastic membrane. The invention also concerns a cuvette which is designed for mixing according to the method.</p> <div style="text-align: right;">  </div>		

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MIXING METHODField of the Invention

The present invention relates to a method for carrying out mixing in thin liquid layers. More specifically, the invention concerns a method for carrying out mixing in disposable devices to permit quantitative and qualitative analyses. The invention also concerns a method for performing such analyses as well as devices which are suited for use when performing the analyses.

10 Background Art

Disposable devices, so-called microcuvettes, are disclosed in, for instance, Patent Publications EP 469 097 and WO 96/33399. These microcuvettes are intended for sampling of liquid, such as blood, mixing of the liquid sample with a reagent and direct optical analysis of the sample mixed with the reagent. The microcuvette comprises a body with a cavity which contains a measuring area. The cavity communicates with the surroundings outside the body through an inlet. Moreover, the cavity has a predetermined volume and is designed in such manner that the sample can enter by capillary force. A dry reagent is applied to the surface of the measuring cavity. Microcuvettes of this type have been commercially successful to a considerable extent and are currently used for quantitative determination of, for instance, haemoglobin and glucose in whole blood. An important factor which has contributed to this success is that the time from sampling to response is very short. One reason for this period of time being very short is that the reagent compositions that are used for determination of haemoglobin and glucose are readily soluble in the small amount of blood that is sucked into the capillary cavity of the microcuvette, which results in a mixing with uniform distribution of the reagent components practically

immediately. However, it has been found that these prior-art microcuvettes are less suitable for determining components that require reagents, which are not readily soluble and/or in which diffusion problems exist and  
5 which therefore require a comparatively long period of time for dissolution and reaction.

A method, which has been developed specifically for mixing a liquid and a reagent in the thin capillary layers that exist in the microcuvettes, has been suggested in US Patent 4,936,687. In this method, use is made  
10 of small magnetic particles as means to accomplish the mixing, and the actual mixing operation is carried out by using outer magnets, which are specially designed and arranged in a special manner and operated in a predetermined fashion. After the mixing procedure, the magnetic  
15 particles are separated from that part of the sample which is to be analysed. Although this method functions well for certain types of liquids/reagents, it is not particularly attractive from an industrial and commercial point of view since special arrangements and designs of  
20 magnets are necessary. The use of fine magnetic particles and the separation of these particles after the mixing step also require time and work, which makes the method complicated and comparatively expensive. Moreover, there  
25 is a risk of chemical obstruction, caused by the magnetic particles, of both samples and reagents.

Furthermore, EP 75 605 discloses a method for mixing in capillary liquid layers. According to this method, the mixing is carried out in a reaction vessel, which comprises two parallel plates which are movable relative to  
30 and towards each other. Just a few microlitres of reagent and sample are applied, when filling the reaction vessel, to particular adhesion surfaces or in various positions within an adhesive surface of the plates, and mixing of  
35 sample and reagent is carried out by moving the plates towards each other and perpendicular to the liquid layer formed by the sample and the reagent. This prior-art

method thus requires that both sample and reagent be present in the form of liquid, which makes it easier to carry out the mixing compared with the above microcuvettes with a dry reagent which besides is difficult to dissolve. This type of mixing, i.e. where the liquid layer is made to move perpendicular to the plane of the layer, has been tested to achieve mixing in microcuvettes of the above type but has not been found to be sufficiently effective.

10       A simple and effective method for mixing of liquid and reagent in thin capillary layers, which is also suitable to accelerate the dissolution of less soluble reagents, would increase the number of determinations that can be carried out in both microcuvettes and devices of the same fundamental design as the microcuvettes. As a result, analyses which up to now could not be performed or for which there has previously been no interest in connection with disposable devices for essentially simultaneous sampling and analysis and with capillary drawing-  
15       in of the sample could also be attractive.

#### Summary of the Invention

According to the invention, mixing is carried out in a capillary liquid layer arranged between two essentially plane-parallel walls by the walls, which are essentially immovable relative to each other, being subjected to a motion essentially in the plane of the liquid layer, balancing the motion against the capillary force exerted by the walls on the liquid and selecting the interface  
25       between the liquid layer and the surrounding medium so that it functions as an elastic membrane. The invention also concerns a disposable device intended for use when carrying out the method and especially in sampling and analysis.

35       This method is well suited to achieve more rapid dissolution of certain dry reagents which are relatively difficult to dissolve, and more efficient mixing of

sample and reagent in the thin liquid layers that are present in disposable devices or microcuvettes of the above type. In principle, however, the mixing method can be applied to all liquids in the form of thin layers  
5 between essentially parallel walls which are arranged at a capillary distance from each other.

#### Detailed Description of the Invention

The capillary force depends on the type of material  
10 of the walls, the type of sample including additives, if any, such as reagents, and the distance between the walls. The frequency and amplitude parameters of the motion must be balanced against the capillary force that is present in the individual case, and these parameters  
15 must be sufficient to provide mixing without any risk that part of the liquid escapes from the microcuvette, which may happen if the frequency/amplitude is too high.

The upper limit of the length of the elastic membrane, i.e. of the interface of the sample towards the  
20 surrounding medium, such as air, is present in the case where the volume of the liquid sample is only limited by the parallel walls and is not enclosed in a cavity. The lower limit is determined experimentally on the basis of sample liquid, reagent, suitable beat frequency, cavity  
25 depth etc.

When the correct conditions for the motion are present, the interface serves as an elastic membrane which forces the chemical compounds in the sample liquid and a reagent composition, if any, which is dissolved or being  
30 dissolved, to move with the liquid motion, which results in a mixing of sample liquid and reagent in the thin liquid layer.

According to the present invention, the mixing is thus carried out by making a device with a liquid layer  
35 of a liquid sample and reagent move essentially in the plane of the liquid layer during a period of time and at a speed which are sufficient to accomplish the desired

mixing. The motion can be rotating but a reciprocating motion is preferred. Any combination of these motions can also be used. As mentioned above, an important feature of the new mixing method is that the motion is  
5 balanced against the capillary force so that the liquid sample does not flow out of the device. The capillary force is determined by the type of sample and the material of the walls of the device, and the balancing operation is preferably made experimentally. As indicated  
10 above, it is a critical feature that the interface between the sample and the surroundings is selected so that this interface can serve as an elastic membrane. The interface between sample and air in the inlet of the disposable device or microcuvette will serve as an elastic  
15 membrane only on the condition that the length of this inlet is sufficient or if the device contains at least one more cavity, which is essentially non-capillary and can form a further elastic membrane. In the latter case, the inlet of the cuvette need not be greater than the  
20 distance between essentially plane-parallel walls which define the measuring cavity, while in the former case, i.e. when the volume of the sample liquid only forms a continuous interface (a continuous membrane) against the surrounding medium (air), the length of the inlet should  
25 be at least 5, preferably at least 10 times greater than the depth of the liquid layer in the measuring cavity.

A microcuvette which is suited for mixing according to the invention, comprises a body with a measuring cavity which is defined by two essentially parallel surfaces,  
30 which define an optical path and are arranged at a predetermined distance from each other. The measuring cavity has a predetermined volume and a capillary inlet connects the cavity with the surroundings outside the body. Under the action of capillary force, the sample is drawn into  
35 the measuring cavity through the inlet. A predetermined amount of dry reagent is arranged in the measuring cavity, e.g. applied to the surface of the cavity. The walls

of the microcuvette are preferably transparent and non-elastic. The volume of the cuvette may vary between 0.1  $\mu$ l and 1 ml and the thickness of the thin layer may vary between 0.01 and 2.00 mm, and preferably between 0.1  
5 and 1.0 mm. The distance between the walls at the inlet or opening of the cuvette can preferably be between 0.01 and 1 mm and is preferably greater than the distance between the walls in the measuring cavity.

The mixing method according to the present invention  
10 is, of course, also suited for mixing in devices which are not intended to be used for optical, for instance, turbidimetric or nephelometric, measurement, but it is generally applicable to mixing in thin liquid layers. Examples of other types of measurements are radioactive  
15 measurements, in which optical path length and transparent walls are not required. In general terms, it may be said that the sampling device is designed in respect of the analysis for which it is intended, and the sampling devices have the common feature that under the action of  
20 capillary force the sample can be drawn into a capillary cavity and mixing of sample and reagent occurs in a capillary liquid layer.

The method for mixing according to the invention is particularly applicable when it is desirable to perform  
25 essentially simultaneous sampling and quantitative determination of a component in a liquid sample in a capillary disposable device, such as a microcuvette. This sampling and determination comprise the steps of

- inserting the sample containing the component to  
30 be determined into a disposable device, which contains at least a dry reagent for the component and into which the sample is drawable under the action of capillary force through an inlet in a capillary cavity, which is defined by two essentially plane-parallel walls,

35 - subjecting the device to a motion to accelerate the dissolution of the reagent and mixing in the thin liquid layer of reagent and sample, said layer being



formed between the plane-parallel walls which define the cavity, the motion occurring essentially in the plane of the liquid layer and being balanced against the capillary force exerted by the walls on the liquid layer, and the  
5 interface between the liquid layer and the surrounding medium being selected so that it functions as an elastic membrane, and

- subjecting the resulting mixture to measurement in a measuring area.

10 An important feature of the mixing method according to the invention is that the motion occurs essentially in the plane of the liquid layer, i.e. that the motion, which preferably can be a reciprocating vibration at an experimentally determined frequency and amplitude, occurs  
15 essentially in parallel with the principal plane of the capillary cavity. Minor deviations from the principal plane can be tolerated, but deviations above 20° from this plane have been found to result in a clearly deteriorated mixing effect.

20 Even if any type of reagent can be applied in the cuvette, special advantages are achieved when using reagents which are comparatively difficult to dissolve, such as proteins and carbohydrates.

The components which are particularly interesting to  
25 analyse in the inventive measuring method are macromolecular compounds such as proteins, for instance albumin or other proteins, e.g. CRP (C-Reactive Protein), with which turbidimetrically measurable antigen-antibody aggregates can be produced. The application of the present invention  
30 may also comprise non-protein-based antigens, such as polysaccharides. The inventive principle can be applied in many contexts where turbidimetric quantification of an analyte can occur. In such optical measurement in a microcuvette, the walls in the measuring area are arranged  
35 ed with a predetermined optical path length.

An example of an analysis where mixing in a microcuvette has extensive practical use, are the analyses

which are based on antigen-antibody reactions, such as in determination of  $\mu$  albumin in urine, in which antibodies against human albumin are made to react with albumin in a urine sample. A predetermined amount of antialbumin-antibodies together with PEG 6000 is supplied to the cavity of the cuvette and dried. When the sample enters the cuvette cavity, which has a predetermined volume and gap width, the reagent is dissolved if the cuvette is made to vibrate at a frequency of 60 beats/s. Albumin which is present in the urine sample, reacts with the dissolved antibodies and forms aggregates, which cause turbidity that can be measured spectrophotometrically at 470 nm and that is proportional to the concentration of albumin in the sample. Correspondingly, analyses can be performed on albumin or some other protein in blood or plasma. A mixing according to the present invention, which preferably is carried out in a spectrophotometer of the type disclosed in Swedish Patent Application 9800072-2, is an important condition for a quick and reproducible response.

According to a preferred embodiment, the essentially non-capillary cavity is arranged adjacent to the capillary measuring cavity containing the dry reagent and is arranged essentially in alignment with the inlet and the measuring cavity. When the liquid sample in this embodiment is drawn into the cuvette and mixed according to the invention, the liquid in the cavity and the medium, usually air, which is present in the non-capillary cavity, form a separate interface which also serves as an elastic membrane.

Inventive measuring cuvettes are illustrated in the accompanying drawings, in which

Fig. 1 is a perspective view of a microcuvette,  
Fig. 2 is a cross-sectional view of the microcuvette in Fig. 1

Fig. 3 is a perspective view of a microcuvette with two cavities, and

Fig. 4 is a cross-sectional view of the microcuvette in Fig. 3.

5

In Fig. 1, 1 designates the microcuvette and 2 the capillary inlet, which, when the sample has been drawn into the cuvette, forms an elastic membrane against the surrounding air.

10 In a corresponding manner, two elastic membranes form against air in the microcuvette illustrated in Figs 3 and 4, in which 3 indicates the capillary inlet and 4 a cavity of a greater depth, which cavity is essentially non-capillary.

15 The agitation according to the invention can be exemplified as follows.

The agitation was studied as a function of cavity depth and beat frequency. Cuvettes having the same design of the cavity were used.

20

Cavity Depth	Beat Frequency (beats/s)	Comments
150 $\mu\text{m}$	60	no agitation
130 $\mu\text{m}$ in measuring eye/400 $\mu\text{m}$ outside	60	agitation in 400 $\mu\text{m}$ no agitation in 130 $\mu\text{m}$
130 $\mu\text{m}$ in measuring eye/400 $\mu\text{m}$ outside	30	no agitation
300 $\mu\text{m}$	60	no agitation
300 $\mu\text{m}$	30	no agitation
500 $\mu\text{m}$	60	good agitation
500 $\mu\text{m}$	30	no agitation
700 $\mu\text{m}$	60	good agitation

The results show that the agitation is dependent on both beat frequency and cavity depth. Thus, good agitation is obtained in a 400- $\mu\text{m}$ -deep cuvette at

10

60 beats/s but not at 30 beats/s. If the depth of the cavity decreases, no agitation occurs.

## CLAIMS

1. A method of carrying out mixing in a thin liquid  
5 layer arranged between essentially parallel walls which  
are essentially immovable relative to each other and  
arranged at a capillary distance from each other, the  
mixing being carried out by subjecting the walls to a  
motion essentially in the plane of the liquid layer,  
10 balancing the motion against the capillary force exerted  
by the walls on the liquid, and selecting the interface  
between the liquid layer and the surrounding medium so  
that it functions as an elastic membrane.

15 2. A method as claimed in claim 1, wherein the  
motion is an essentially reciprocating motion.

3. A device (1) for carrying out mixing in a thin  
liquid layer as claimed in claim 1 or 2, into which  
20 device a liquid sample is drawable under the action of  
capillary force through an inlet (2, 3) in a capillary  
cavity, which connects the inlet (2, 3) of the device  
with the surroundings outside the device (1) and in which  
a dry reagent is applied, wherein the distance between  
25 two essentially parallel walls which are essentially  
immovable relative to each other and which define the  
cavity, is at most 1000  $\mu\text{m}$ , preferably between 400  $\mu\text{m}$   
and 600  $\mu\text{m}$ , and the length of the inlet is at least 5,  
preferably at least 10 times greater than the distance  
30 between the walls.

4. A device (1) for carrying out mixing in a thin  
liquid layer as claimed in claim 1 or 2, into which  
device a liquid sample is drawable under the action of  
35 capillary force through an inlet (2, 3) in a capillary  
cavity, which connects the inlet (2, 3) of the device  
with the surroundings outside the device (1) and in which

a dry reagent is applied, wherein the distance between two essentially parallel walls which are essentially immovable relative to each other and which define the cavity, is at most 1000  $\mu\text{m}$ , preferably between 400  $\mu\text{m}$  and 600  $\mu\text{m}$ , and wherein an essentially non-capillary cavity (4) is arranged adjacent to the capillary cavity and essentially in alignment with the inlet (3) and the measuring cavity.

10           5. A device (1) as claimed in claim 3 or 4, characterised in that the plane-parallel walls are transparent and essentially non-elastic.

15           6. A method for essentially simultaneous sampling and quantitative determination of a component in a liquid sample, comprising the steps of

20           - inserting the sample containing the component to be determined into a disposable device, which contains at least a dry reagent for the component and into which the sample is drawable under the action of capillary force through an inlet in a capillary cavity, which is defined by two essentially plane-parallel walls, said inlet connecting the cavity with the surroundings outside the disposable device,

25           - subjecting the device to a motion to accelerate the dissolution of the reagent and mixing in the thin liquid layer of reagent and sample, said layer being formed between the plane-parallel walls which define the cavity, the motion occurring essentially in the plane of the liquid layer and being balanced against the capillary force exerted by the walls on the liquid, and the interface between the liquid layer and the surrounding medium being selected so that it functions as an elastic membrane, and

35           - subjecting the resulting mixture to measurement.

7. A method as claimed in claim 6, c h a r a c -  
t e r i s e d in that the component is a macromolecular  
compound, such as a protein or a carbohydrate.

5        8. A method as claimed in claim 6, c h a r a c -  
t e r i s e d in that the reagent is an antibody or a  
lectin.

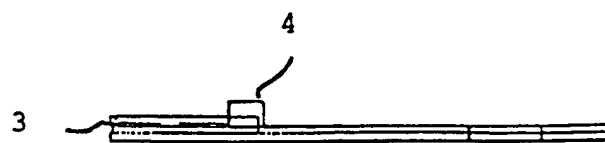
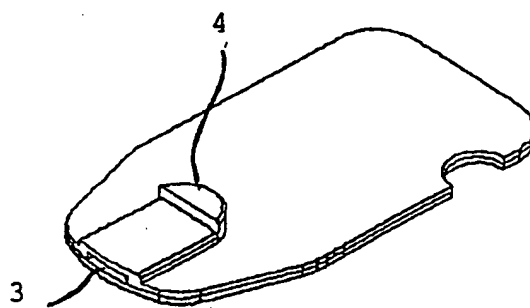
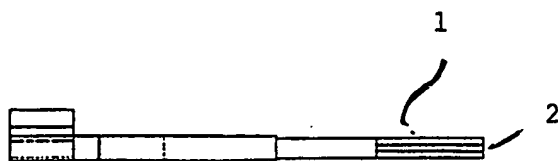
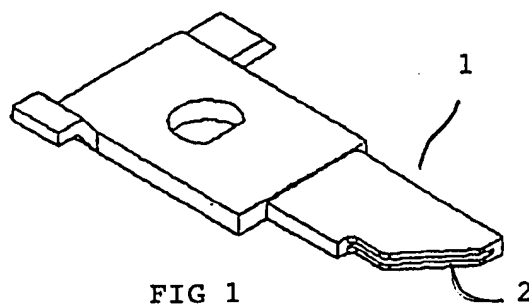
10       9. A method as claimed in any one of claims 6-8,  
c h a r a c t e r i s e d in that in mixing, the reagent  
and the macromolecular compound form an aggregate which  
consists of an antibody-antigen complex or a lectin-car-  
bohydrate complex.

15       10. A method as claimed in claim 7, c h a r a c -  
t e r i s e d in that the macromolecular compound con-  
sists of a plasma protein, such as albumin or a C-Reac-  
tive Protein (CRP).

20       11. A method as claimed in any one of claims 6-9,  
wherein the motion is an essentially reciprocating  
motion.

25       12. A method as claimed in any one of the preceding  
claims, c h a r a c t e r i s e d in that the measurement  
is an optical measurement.

30       13. A method as claimed in claim 7, c h a r a c -  
t e r i s e d in that the optical measurement is a tur-  
bidimetric or nephelometric measurement.





## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00046

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: G01N 21/03, B01L 3/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: G01N, B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ, TXTE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0803288 A2 (KYOTO DAIICHI KAGAKU CO., LTD.), 29 October 1997 (29.10.97), column 12, line 16 - line 33; column 15, line 50 - column 16, line 20; column 19, line 45 - column 20, line 5, column 21, line 36 - 42; column 24, line 22 - line 41; figure 1A, 1B; abstract --	3-5
X	US 5658723 A (BRUCE OBERHARDT), 19 August 1997 (19.08.97), column 5, line 5 - column 7, line 2; column 14, line 42 - line 47 --	3-5
X	EP 0287883 A1 (MILES INC.), 26 October 1988 (26.10.88), column 7, line 6 - column 9, line 6 --	3-5

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

22 April 1999

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00046

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0075605 A1 (STÖCKER, WINFRIED), 6 April 1983 (06.04.83), page 12, line 11 - page 13, line 18, figure 3002,3002, claim 1 --	1-2,6-13
A	US 18435 A1 (STÖCKER, WINFRIED), 12 November 1980 (12.11.80), page 3, line 26 - page 4, line 6, claims 1,5,6 --	1-2,6-13
A	US 4088448 A (JAN EVERT LILJA ET AL), 9 May 1978 (09.05.78) -- -----	6-13

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Information on patent family members

02/03/99

International application No.

PCT/SE 99/00046

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DE	107783	C	12/08/74	NONE			
EP	0075605	A1	06/04/83	AT	25009	T	15/02/87
US	18435	A1	12/11/80	NONE			
US	4088448	A	09/05/78	AT	376300	B	25/10/84
				AT	683876	A	15/03/84
				AU	497567	B	14/12/78
				AU	1822976	A	06/04/78
				BE	846403	A	17/01/77
				BR	7606475	A	28/06/77
				CA	1057078	A	26/06/79
				CH	612505	A	31/07/79
				DE	2641097	A,C	07/04/77
				DK	150804	B,C	22/06/87
				DK	435376	A	30/03/77
				FI	59672	B,C	29/05/81
				FI	762737	A	30/03/77
				FR	2325920	A,B	22/04/77
				GB	1557984	A	19/12/79
				HK	18083	A	03/06/83
				IE	43188	B	31/12/80
				IN	145819	A	30/12/78
				JP	1125827	C	30/11/82
				JP	52055679	A	07/05/77
				JP	57011414	B	04/03/82
				JP	57066343	A	22/04/82
				LU	75854	A	04/05/77
				NL	181381	B,C	02/03/87
				NL	7610712	A	31/03/77
				SE	399768	B,C	27/02/78
				SE	7510863	A	30/03/77